DRUG-RESISTANCE TESTING (Updated January 10, 2011)

Panel's Recommendations:

- ***HIV drug-resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred (AIII). If therapy is deferred, repeat testing at the time of ART initiation should be considered (CIII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naïve patients (AIII).***
- ***Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with genotypic testing for resistance to this class of drug (CIII).***
- ***HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and HIV RNA levels >1,000 copies/mL (AI). In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII).***
- ***Drug-resistance testing should also be performed when managing suboptimal viral load reduction (AII).***
- ***In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include a drug from this class in subsequent regimens (BIII).***
- ***Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy (AII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).***
- ***Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs) (BIII).***
- ***Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Genotypic and Phenotypic Resistance Assays

Genotypic and phenotypic resistance assays are used to assess viral strains and inform selection of treatment strategies. Standard assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Testing for integrase and fusion inhibitor resistance can also be ordered separately from several commercial laboratories. No genotypic assays for assessing resistance to CCR5 antagonists are currently commercially available for clinical use in the United States. (See **Coreceptor Tropism Assays**.)

Genotypic Assays

Genotypic assays detect drug-resistance mutations present in relevant viral genes. Most genotypic assays involve sequencing of the RT and PR genes to detect mutations that are known to confer drug resistance. Genotypic assays that assess mutations in the integrase and gp41 (envelope) genes are also commercially available. Genotypic assays can be performed rapidly with results available within 1–2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations that different ARV drugs select for and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains a list of updated significant resistance-associated mutations in the RT, PR, integrase, and envelope genes (see **http://www.iasusa.org/resistance_mutations**) *[1]*. The Stanford University HIV Drug Resistance Database (**http://hivdb.stanford.edu**) also provides helpful guidance for interpreting genotypic resistance test results. Various tools are now available to assist the provider in interpreting genotypic test results *[2-5]*. Clinical trials have demonstrated the benefit of consultation with specialists in HIV drug resistance in improving virologic outcomes *[6]*.

Clinicians are thus encouraged to consult a specialist to facilitate interpretation of genotypic test results and the design of an optimal new regimen.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT and PR gene sequences and, more recently, integrase and envelope sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration $[IC]_{50}$) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance).

Automated phenotypic assays are commercially available with results reported in 2–3 weeks. However, phenotypic assays cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs *[7-11]*. Again, consultation with a specialist can be helpful for interpreting test results.

Further limitations of both genotypic and phenotypic assays include lack of uniform quality assurance for all available assays, relatively high cost, and insensitivity for minor viral species. Despite being present, drug-resistant viruses constituting less than 10%–20% of the circulating virus population will probably not be detected by available assays. This limitation is important because after drugs exerting selective pressure on drug-resistant populations are discontinued, a wild-type virus often re-emerges as the predominant population in the plasma. As a consequence, the proportion of virus with resistance mutations decreases to below the 10%–20% threshold *[12-14]*. For some drugs, this reversion to predominantly wild-type virus can occur in the first 4–6 weeks after drugs are stopped. Prospective clinical studies have shown that, despite this plasma reversion, reinstitution of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and the virus present at failure is derived from previously archived resistant virus *[15]*. Therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued **(AII)**. Because detectable resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing beyond 4 to 6 weeks after discontinuation may still reveal mutations. However, the absence of detectable resistance in such patients must be interpreted with caution in designing subsequent ARV regimens.

Use of Resistance Assays in Clinical Practice (Table 4)

No definitive prospective data exist to support using one type of resistance assay over another (i.e., genotypic vs. phenotypic) in different clinical situations. In most situations genotypic testing is preferred because of the faster turnaround time, lower cost, and enhanced sensitivity for detecting mixtures of wild-type and resistant virus. However, for patients with a complex treatment history, results derived from both assays might provide critical and complementary information to guide regimen changes.

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial ART *[16-19]*. The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in HIV-infected persons engaging in high-risk behaviors in the community. In the United States and Europe, recent studies suggest the risk that transmitted virus will be resistant to at least one ARV drug is in the range of 6%–16% *[20-25],* with 3%–5% of transmitted viruses exhibiting resistance to drugs from more than one class *[16, 24]*.

If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will provide guidance in selecting a regimen to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AIII)** and a genotypic assay is preferred **(AIII)**. In this setting, treatment initiation should not be delayed by pending resistance testing results. Once results are obtained, the treatment regimen can be modified if warranted by the results. (See **Acute HIV Infection**.) In the absence of therapy, resistant viruses may decline over

time to less than the detection limit of standard resistance tests but may still increase the risk of treatment failure when therapy is eventually initiated *[26-28]*. Therefore, if therapy is deferred, resistance testing during acute HIV infection should still be performed **(AIII)**. In this situation, the genotypic resistance test result might be kept on record for several years before it becomes clinically useful. Because it is possible for a patient to acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of ART, repeat resistance testing at the time treatment is started should be considered **(CIII)**.

Performing drug-resistance testing before ART initiation in patients with chronic HIV infection is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure, and it is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier *[29-31]*. No prospective trial has addressed whether drug-resistance testing prior to initiation of therapy confers benefit in this population. However, data from several, but not all, studies suggest suboptimal virologic responses in persons with baseline mutations *[16-19, 32-34]*. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed *[35]*. Therefore, resistance testing in chronically infected persons at the time of entry into HIV care is recommended **(AIII)**. Genotypic testing is generally preferred in this situation because of lower cost, more rapid turnaround time, ability to detect mixtures of wild-type and resistant virus, and the relative ease of interpretation **(AIII)**. If therapy is deferred, repeat testing just prior to initiation of ART should be considered because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the RT and PR genes. Although transmission of INSTI-resistant virus has rarely been reported, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, providers may wish to supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs **(CIII).**

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding decisions for patients experiencing virologic failure while on ART. Several prospective studies assessed the utility of resistance testing in guiding ARV drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both *[6, 36-42]*. In general, these studies found that early virologic response to salvage regimens was improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Additionally, one observational study demonstrated improved survival in patients with detectable HIV plasma RNA when drug-resistance testing was performed *[43]*. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing ARV regimens for virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)**. (See **Virologic and Immunologic Failure**.) In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Drug-resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL because resistance assays cannot be consistently performed given low HIV RNA levels **(AIII)**.

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination ART is, for certain patients, associated with resistance to only one component of the regimen *[44-46]*. In that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation. (See **Virologic and Immunologic Failure**.)

Genotypic testing is generally preferred for virologic failure or suboptimal viral load reduction in persons failing their first or second ARV drug regimen because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus **(AIII)**. Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to PIs **(BIII)**.

In patients failing INSTI-based regimens, testing for INSTI resistance should be considered to determine whether to include drugs from this class in subsequent regimens; genotypic testing is preferred **(BIII)**. Although it is not a drug-resistance assay, a coreceptor tropism assay should be performed whenever the use of a CCR5 antagonist is being considered **(AI)**. Coreceptor tropism testing should also be considered for patients who exhibit virologic failure on a CCR5 antagonist **(CIII)**. However, such testing may be of limited value because the absence of detectable CXCR4-

using virus does not exclude the possibility that CCR5 antagonist resistance may have developed. Assays for resistance to CCR5 inhibitors are not yet commercially available *[47]*. (See **Coreceptor Tropism Assays**.)

Use of Resistance Assays in Pregnant Women

In pregnant women, the goal of ART is to maximally reduce plasma HIV RNA to provide appropriate maternal therapy and prevent mother-to-child transmission (MTCT) of HIV. Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Phenotypic testing may provide additional information in those found to have complex drug-resistance mutation patterns, particularly to PIs **(BIII)**. Optimal prevention of perinatal transmission may require initiation of ART while results of resistance testing are pending. Once the results are available, the ARV regimen can be changed as needed.

Table 4. Recommendations for Using Drug-Resistance Assays (Updated January 10, 2011)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug-resistance testing is recommended regardless of whether ART is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is to be initiated immediately, drug-resistance testing will determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or to modify or change regimens if results are obtained subsequent to treatment initiation. Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat resistance testing should be considered at the time therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naïve patients with chronic HIV infection: Drug-resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least one drug is seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated chronically infected patients.
If therapy is deferred, repeat resistance testing should be considered prior to the initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing prior to initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If an INSTI is considered for an ART-naïve patient and transmitted INSTI resistance is a concern, providers may wish to supplement standard resistance testing with a specific INSTI genotypic resistance assay **(CIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.

Table 4. Recommendations for Using Drug-Resistance Assays

Clinical Setting/Recommendation	Rationale
In patients with virologic failure: Drug-resistance testing is recommended in persons on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.	Testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy.
A standard genotypic resistance assay is generally preferred for those experiencing virologic failure on their first or second regimens **(AIII)**.	Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
In patients failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include drugs from this class in subsequent regimens **(BIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
Addition of phenotypic assay to genotypic assay is generally preferred for those with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**.	Phenotypic testing can provide useful additional information for those with complex drug-resistance mutation patterns, particularly to PIs.
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended for persons with suboptimal suppression of viral load after initiation of ART **(AII)**.	Testing can help determine the role of resistance and thus assist the clinician in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women prior to initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug-resistance assay not usually recommended	
After therapy discontinued: Drug-resistance testing is not usually recommended after discontinuation (>4 weeks) of ARV drugs **(BIII)**.	Drug-resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

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